Remarks

Claims 7, 26-29 and 32 are pending in the subject application. By this Amendment, Applicants have amended claim 7 to require that the PXRD pattern is obtainable by a technique employing a rotating sample tube. Support for the amendment can be found at least at pages 37-38 of the specification. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 7, 26-29 and 32 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 103(a) (over Talley *et al.* in view of Rubino *et al.*).

Claims 7, 26-29, and 32 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has presented an analysis under *In re Wands* in arguing that the presently claimed invention is not enabled. With regard to the state of the art, Rubino *et al.* teach that sodium salts of sulfonamides crystallized in the presence of propylene glycol and water may crystallize in the form of hydrates and that all the sulfonamide compounds tested formed crystal hydrates and not solvates. The Office Action also states that Brittain *et al.* teach that (1) pharmaceutical solids that come into contact with water may form hydrates, (2) exposure of a crystal solvate to water vapor may result in formation of a hydrate, (3) hydrates may be obtained from mixed solvent systems, (4) a pharmaceutical compound may produce a broad scope of possible hydrate and solvate forms, and (5) crystallization is highly unpredictable and requires an empirical approach. Finally, the Office Action states that Davidovich *et al.* teach that severe preferential organization can degrade the utility of XRD powder data, that small changes in X-ray powder patterns may falsely imply a new crystalline form, and that minor variations can result in significant modifications of crystal form. Applicants respectfully assert that the claims as filed are enabled and traverse the rejection.

Applicants assert that even if Rubino *et al.* do teach that certain sulfonamides did not form solvates under the conditions used by Rubino *et al.*, one of skill in the art would give such information little or no credence in determining whether the instant invention is enabled. First, the sulfonamides disclosed by Rubino *et al.* are all of strikingly similar structure to one another (*i.e.*, *para*-amino-phenyl-sulfonamide-heteroaryl), but that structure is not shared by celecoxib.

Accordingly, one would not have any expectation that celecoxib would behave like the sulfonamides of Rubino *et al.*

Second, Rubino *et al.* disclose a process involving a mixed solvent system in which propylene glycol is 50% or less by weight in relation to water. Given the differing molecular weights of water and propylene glycol, this represents at least a 4:1 molar excess of water. In contrast, Applicants disclose methods wherein water is present, if at all, only as a minor contaminant. Additionally, one of skill in the art would expect that increasing the solvent:water ratio would typically favor formation of solvate over hydrate. Indeed, Brittain *et al.* provide support for such an expectation. Brittain *et al.*, at page 207, state that in most cases when one recrystallizes a hydrate from dry methanol, one is left with a methanol solvate or an anhydrous form (despite, one presumes, the presence of a small amount of contaminating water originally present in the hydrate itself). The fact that Brittain *et al.* acknowledge at page 203 that "in some instances" crystal solvates may be converted to hydrates in a humid atmosphere is not surprising – an "atmosphere containing water vapor" may provide an abundant source of water that favors the formation of the hydrate. Accordingly, one of ordinary skill would expect that the results of Rubino *et al.* are at best marginally relevant to the enablement analysis with respect to the presently claimed invention.

With respect to the statement that Brittain *et al.* teach that (1) pharmaceutical solids that come into contact with water may form hydrates, (2) exposure of a crystal solvate to water vapor may result in formation of a hydrate, and (3) hydrates may be obtained from mixed solvent systems, Applicants respond that even if taken as true, none of these teachings suggest that water automatically or in all cases displaces the molecules of other solvents to convert crystal solvates to crystal hydrates. One of skill in the art would be more likely to understand Brittain *et al.* as discussing the fact that water is merely one type of solvent and that it may be favored to displace another type of solvent molecule if (1) it happens to have a higher affinity for a particular solid or (2) it has a lower affinity but is nevertheless favored due to being present at a much higher concentration than the other solvent. For example, Applicants attach, for the Examiner's consideration, a journal article (Kacperska, *J Thermal Analysis*, 1993, Vol. 40, pp. 419-426) wherein it is disclosed that solid solvates of NaI vary according to the relative concentrations of the two solvents in a mixed solvent system. In a mixed water/DMF solvent system, solid hydrates of NaI were preferred only in the

"water rich region" (*i.e.*, DMF < 25% in the solvent mixture). Mixed solid solvates of NaI (*i.e.*, incorporating both water and DMF in the solid) were observed when the solvent was in the range of 25% to 80% DMF. Finally, at concentrations above 80% DMF, the solid solvate contained DMF only and no water. Thus, it is clear that the amount of solvent present in the system strongly influences the formation of a solvate. In this case, given that water is present, if at all, only as a contaminant in the claimed solvates, one of skill in the art would consider it quite unlikely that celecoxib forms a solid hydrate instead of a solid propylene glycol solvate.

With regard to the statement that Davidovich *et al.* teach that severe preferential organization can degrade the utility of XRD powder data and that small changes in X-ray powder patterns may falsely imply a new crystalline form, Applicants submit that Davidovich *et al.* teach that the XRD powder data of Applicants is highly reliable. Although Davidovich *et al.* may teach that certain XRD techniques may be unreliable, they also teach that rotating a capillary containing the sample overcomes these problems (see page 12, first column, third paragraph (indicating that grinding can often minimize artifacts but in some cases a rotating capillary method must be used) and page 16, second column, second paragraph (discussing – and showing in Figure 10 – that capillary rotation produces a PXRD pattern that is in "very good agreement" with the theoretical simulated pattern despite using suboptimal unground sample)). Applicants note that the specification, at pages 37-38, establishes that PXRD was performed using a rotating capillary; thus, one of skill in the art would recognize that Applicants employed an analysis technique that avoids the problems taught by Davidovich *et al.*

With respect to the breadth of the claims, the Examiner indicates that the scope of the claims is "infinite" because "any possible sample preparation technique and analytical instrument could potentially be used to characterize said form of a propylene glycol solvate of celecoxib." In response, Applicants assert that the claims are of appropriate scope. As an initial point, Applicants note that the claims are drawn to a composition of matter, not to a method. Accordingly, it is irrelevant to the enablement inquiry whether there is one way or many ways to obtain the claimed composition(s). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987). The Examiner also indicates that

Brittain *et al.* teach that a pharmaceutical compound may produce a broad scope of possible hydrate and solvate forms, but Applicants do not claim all possible hydrate and solvate forms. Applicants claim specific forms of a propylene glycol solvate of celecoxib and the claims are limited by structural parameters (*i.e.*, characterized by PXRD peak). Accordingly, Applicants believe that the claims are of appropriate and limited scope and that enablement is thus commensurate in scope with the claims.

With regard to the statements that Brittain *et al.* teach that crystallization is highly unpredictable and requires an empirical approach, Applicants assert that the as-filed specification fully enables the claimed propylene glycol solvates of celecoxib (see, for example, Examples 1-3 and 7). Moreover, Applicants have reproducibly demonstrated success in obtaining propylene glycol solvate forms of celecoxib. Indeed, Examples 1-3 employ similar techniques to obtain propylene glycol solvate forms of various metal salts (sodium, potassium, lithium) of celecoxib. In each, the celecoxib is dissolved in diethyl ether, propylene glycol is added, an alkyl or alkoxide salt is added to form the celecoxib salt, and a solid crystallizes in 5-10 minutes. In light of the evidence that strongly supports that Applicants have obtained propylene glycol solvate forms and have done so with repeated success, Applicants assert that the invention is enabled. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

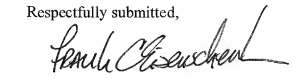
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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